Stimulation of the stress-activated mitogen-activated protein kinase subfamilies in perfused heart. p38/RK mitogen-activated protein kinases and c-Jun N-terminal kinases are activated by ischemia/reperfusion.

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It has recently been recognized that cellular stresses activate certain members of the mitogen-activated protein kinase (MAPK) superfamily. One role of these "stress-activated" MAPKs is to increase the transactivating activity of the transcription factors c-Jun, Elk1, and ATF2. These findings may be particularly relevant to hearts that have been exposed to pathological stresses. Using the isolated perfused rat heart, we show that global ischemia does not activate the 42- and 44-kD extracellular signal-regulated (protein) kinase (ERK) subfamily of MAPKs but rather stimulates a 38-kD activator of MAPK-activated protein kinase-2 (MAPKAPK2). This activation is maintained during reperfusion. The molecular characteristics of this protein kinase suggest that it is a member of the p38/reactivating kinase (RK) group of stress-activated MAPKs. In contrast, stress-activated MAPKs of the c-Jun N-terminal kinase (JNK/SAPKs) subfamily are not activated by ischemia alone but are activated by reperfusion following ischemia. Furthermore, transfection of ventricular myocytes with activated protein kinases (MEKK1 and SEK1) that may be involved in the upstream activation of JNK/ SAPKs induces increases in myocyte size and transcriptional changes typical of the hypertrophic response. We speculate that activation of multiple parallel MAPK pathways may be important in the responses of hearts to cellular stresses.

Publication Types:
- Review
- Review, Tutorial

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1: Biochem Biophys Res Commun 1997 Oct 29;239(3):840-4

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Hypoxia and hypoxia/reoxygenation activate p65PAK, p38 mitogen-activated protein kinase (MAPK), and stress-activated protein kinase (SAPK) in cultured rat cardiac myocytes.

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We previously reported that both hypoxia and hypoxia followed by reoxygenation (hypoxia/reoxygenation) rapidly activate Src family tyrosine kinases and p21ras in cultured rat cardiac myocytes. This was followed by the sequential activation of mitogen-activated protein kinase kinase kinase (MAPKKK) activity of Raf-1, MAP kinase kinase (MAPKK), MAPKs (p44mapk and p42mapk, also called extracellular signal-regulated protein kinase [ERK]1 and ERK2, respectively), and S6 kinase (p90rsk). In this study, we demonstrated that both hypoxia and hypoxia/reoxygenation caused rapid activation of stress-activated MAPK signaling cascades involving p65PAK, p38MAPK, and SAPK. These stimuli also caused phosphorylation of activating transcription factor (ATF)-2. Because p65PAK is known to be upstream of p38MAPK and also be a target of p21rac-1, which belongs to the rho subfamily of p21ras-related small GTP-binding proteins, these results strongly suggested that two different stress-activated MAPK pathways distinct from the classical MAPK pathway were activated in response to hypoxia and hypoxia/reoxygenation in cardiac myocytes.

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1: J Immunol 1998 Jul 1;161(1):467-73 Related Articles, NEW Books, LinkOut

Erratum in:

- J Immunol 1999 Mar 1;162(5):3105

SB 203580 inhibits p38 mitogen-activated protein kinase, nitric oxide production, and inducible nitric oxide synthase in bovine cartilage-derived chondrocytes.

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Nitric oxide (NO) is implicated in a number of inflammatory processes and is an important mediator in animal models of rheumatoid arthritis and in in vitro models of cartilage degradation. The pyridinyl imidazole SB 203580 inhibits p38 mitogen-activated protein (MAP) kinase in vitro, blocks proinflammatory cytokine production in vitro and in vivo, and is effective in animal models of arthritis. The purpose of this study was to determine whether SB 203580 could inhibit p38 MAP kinase activity, NO production, and inducible NO synthase (iNOS) in IL-1 stimulated bovine articular cartilage/chondrocyte cultures. The results indicated that SB 203580 inhibited both IL-1 stimulated p38 MAP kinase activity in isolated chondrocytes and NO production in bovine chondrocytes and cartilage explants with an IC50 value of approximately 1 microM. To inhibit NO production, SB 203580 had to be present in cartilage explant cultures during the first 8 h of IL-1 stimulation, and activity was lost when it was added 24 h following IL-1. SB 203580 did not inhibit iNOS activity, as measured by the conversion of arginine to citrulline, when added directly to cultures where the enzyme had already been induced, but had to be present during the induction period. Using a 372-bp probe for bovine iNOS we demonstrated inhibition of IL-1-induced mRNA by SB 203580 at both 4 and 24 h following IL-1 treatment. The iNOS mRNA levels were consistent with NO levels in 24-h cell culture supernatants of the IL-1-stimulated bovine chondrocytes used to obtain the RNA.

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Pharmacological profile of SB 203580, a selective inhibitor of cytokine suppressive binding protein/p38 kinase, in animal models of arthritis, bone resorption, endotoxin shock and immune function

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SB 203580 [4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4- pyridyl)imidazole], a selective cytokine suppressive binding protein/p38 kinase inhibitor, was evaluated in several models of cytokine inhibition and inflammatory disease. It was demonstrated clearly to be a potent inhibitor of inflammatory cytokine production in vivo in both mice and rats with IC50 values of 15 to 25 mg/kg. SB 203580 possessed therapeutic activity in collagen-induced arthritis in DBA/LACJ mice with a dose of 50 mg/kg resulting in significant inhibition of paw inflammation and serum amyloid protein levels. Antiarthritic activity was also observed in adjuvant-induced arthritis in the Lewis rat when SB 203580 was administered p.o. at 30 and 60 mg/kg. Evidence for disease-modifying activity in this model was indicated by an improvement in bone mineral density and by histological evaluation. Additional evidence for beneficial effects on bone resorption was provided in the fetal rat long bone assay in which SB 203580 inhibited 45Ca release with an IC50 of 0.6 microM. In keeping with the inhibitory effects on lipopolysaccharide-induced tumor necrosis factor-alpha in mice, SB 203580 was found to reduce mortality in a murine model of endotoxin-induced shock. In immune function studies in mice treated with SB 203580 (60 mg/kg/day for 2 weeks), there was some suppression of an antibody response to ovalbumin, whereas cellular immune functions measured ex vivo were unaffected. This novel profile of activity strongly suggests that cytokine inhibitors could provide significant benefit in the therapy of chronic inflammatory disease.

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